

## REVIEW

# Temozolomide in aggressive pituitary adenomas and carcinomas

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Temozolomide is an alkylating agent used in the treatment of gliomas and, more recently, aggressive pituitary adenomas and carcinomas. Temozolomide methylates DNA and, thereby, has antitumor effects. O<sup>6</sup>-methylguanine-DNA methyltransferase, a DNA repair enzyme, removes the alkylating adducts that are induced by temozolomide, thereby counteracting its effects. A Medline search for all of the available publications regarding the use of temozolomide for the treatment of pituitary tumors was performed. To date, 46 cases of adenohypophyseal tumors that were treated with temozolomide, including 30 adenomas and 16 carcinomas, have been reported. Eighteen of the 30 (60%) adenomas and 11 of the 16 (69%) carcinomas responded favorably to treatment. One patient with multiple endocrine neoplasia type 1 and an aggressive prolactin-producing adenoma was also treated and demonstrated a good response. No significant complications have been attributed to temozolomide therapy. Thus, temozolomide is an effective treatment for the majority of aggressive adenomas and carcinomas. Evidence indicates that there is an inverse correlation between levels of O<sup>6</sup>-methylguanine-DNA methyltransferase immunoexpression and therapeutic response. Alternatively, high-level O<sup>6</sup>-methylguanine-DNA methyltransferase immunoexpression correlates with an unfavorable response. Here, we review the use of temozolomide for treating pituitary neoplasms.

**KEYWORDS:** Pituitary adenoma; Pituitary carcinoma; MGMT; Temozolomide; Review.

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## INTRODUCTION

Patients with aggressive pituitary adenomas are difficult to clinically manage. Frequently, these adenomas are large, rapidly growing and invasive to their surroundings. These tumors also present problems due to incomplete resection and recurrence. Reoperation, pharmacological treatment and radiotherapy are routinely employed, often in combination. Nevertheless, many patients experience tumor regrowth (1). Endocrinologically active adenomas, particularly prolactin (PRL)- and growth hormone (GH)-producing tumors, may become resistant to medical therapy, thus requiring multiple resections. Radiation and conventional chemotherapy are often employed in an attempt to achieve local tumor control, but the results are often disappointing.

Pituitary carcinomas are rare and present particular diagnostic and therapeutic challenges. All of these

carcinomas are of large size, invasive and associated with craniospinal and/or systemic metastases. Multiple treatment approaches, including surgery, external beam radiotherapy, radiosurgery, adjuvant pharmacological therapy and various chemotherapeutic approaches, are palliative at best, achieving only temporary effects (2,3). Progression of the disease after the diagnosis of pituitary carcinoma is variable but often inexorable. Approximately 75% of patients with systemic metastasis die within 1 year of documented spread (4).

Recent publications have reported the efficacy of temozolomide for treating aggressive pituitary adenomas and carcinomas (5–29). In this review, we discuss the indications, results and side effects of temozolomide therapy.

## Temozolomide

Temozolomide is a second-generation alkylating chemotherapeutic agent related to a series of imidazotetrazines that were originally synthesized in 1987 (30). Orally administered, it readily crosses the blood-brain barrier. At physiological pH, it undergoes rapid conversion to methyltriazeno-imidazole-carboxamide (MTIC), the active agent. It exerts its cytotoxic effects through methylation of DNA at the O<sup>6</sup> position of guanine (31), which then mispairs with

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thymine during the next cycle of DNA replication. The sequence of mismatch-repair events lead to apoptosis.

Temozolomide is accepted as an essential component of adjuvant therapy for the treatment of glioblastoma multiforme and other tumors of the central nervous system (32–34). Recent reports indicate its efficacy for treating advanced-stage malignant neuroendocrine neoplasia (35), melanoma (36,37), and colorectal carcinoma (38).

The standard therapeutic dose of temozolomide is 150–200 mg/m<sup>2</sup> for five of every 28 days (5/28). Depletion of O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT) has been proposed as a means of tumor response to temozolomide (39). Experimental and clinical data have shown that the temozolomide response is schedule-dependent and that alternative dosing regimens may enhance its efficacy (40,41). The anti-angiogenic effect of temozolomide can be optimized by administering low doses of the drug on a frequent or continuous schedule without extended interruptions (i.e., “metronomic” chemotherapy). Temozolomide can also be administered on a continuous, daily metronomic schedule, thus achieving MGMT depletion and improving the clinical response. This dose is generally 50 mg/m<sup>2</sup>/day without interruption (28/28). Other temozolomide schedules recommend administration every other week (7/14) or a 21-consecutive-day regimen that is administered every 28 days (21/28). Both are considered dose-dense regimens based on the Norton-Simon model of cell proliferation, which states that a dose of chemotherapy will have a fixed cell-kill rate regardless of the size of the tumor (39). Thus, decreasing the time interval between doses (i.e., increasing the dose density) improves efficacy by minimizing the opportunity for cellular regrowth between cycles (41). In these dose-dense regimens, temozolomide is administered at a dose of 150 mg/m<sup>2</sup>/day for 7 days every other week (7/14) or at a dose of 85–100 mg/m<sup>2</sup>/day for 21 consecutive days (21/28) (40). In reported pituitary cases, temozolomide was administered as monotherapy in all but three cases. The standard 5/28 regimen was used in almost all instances except in the series of Bush et al. (23), in which a dose-dense, 21/28 schedule was used, and one case progressed to carcinoma, which was then treated using the metronomic 28/28 schedule (29). Temozolomide absorption is only minimally affected by food. Furthermore, no serious side effects have been reported. Common, non-hematological adverse effects are present, including nausea, vomiting, fatigue, headache and constipation, most of which are mild to moderate in severity.

As previously stated, MGMT is a DNA repair protein that reverses the effects of temozolomide therapy (42) by removing alkylating adducts, thereby counteracting its effects (43) and conferring resistance to the agent (44). Low-level expression in a wide variety of human tumors is thought to result from epigenetic silencing by hypermethylation of the MGMT gene promoter (44,45). Low-level MGMT expression is a predictive marker of a favorable clinical outcome in patients with temozolomide-treated glioblastomas (46–48). Herein, we extend this observation to aggressive adenohypophyseal tumors.

### Pituitary adenomas

The first temozolomide-treated pituitary adenoma patient was reported in 2006 (7,8). The tumor, which was investigated using histological, immunohistochemical and electron microscopic techniques, showed significant post-therapeutic effects, including hemorrhage, necrosis, focal

fibrosis, reduced mitotic activity, Ki-67 labeling and, surprisingly, neuronal transformation. MGMT immunorepression was completely absent. Subsequently, the case of a 41-year-old patient with an aggressive silent subtype 2 corticotroph adenoma was reported (10). It showed no morphological changes after temozolomide treatment. The tumor cell nuclei were immunopositive for MGMT. Based upon these results, it was suggested that MGMT immunorepression may predict the responsiveness of temozolomide therapy (10).

To the best of our knowledge, to date 30 cases of pituitary adenoma have been treated with temozolomide (7-16,18-20,22-26,28,29). Patient ages varied from 20 to 71 years (mean: 51 years). Aside from one tumor that was incidentally discovered in a patient with concomitant glioblastoma multiforme, all tumors were morphologically studied. The group included ten adrenocorticotrophic hormone (ACTH)-producing tumors, nine PRL-producing tumors, seven clinically non-functioning adenomas, two silent ACTH adenomas, and two GH-producing adenomas. The time between clinical presentation and onset of temozolomide treatment was between 2 and 23 years (mean: 10.7 years). Twenty-six of the 30 tumors had been irradiated previously. Aside from the incidentally discovered tumor in one patient, all other patients had undergone at least one operative procedure, the number ranging from 0 to 6 procedures (mean: 2.7). The response rate was 60% (18/30 patients). Debono et al. (11) reported the first case of a pituitary adenoma associated with multiple endocrine neoplasia type 1 (MEN1) that was treated with temozolomide. The 47-year-old man had primary hyperparathyroidism and a lesion at the head of the pancreas. Genetic analysis confirmed MEN1. The dopamine-resistant, prolactin-producing pituitary adenoma responded dramatically to temozolomide, demonstrating clinical, biochemical, and radiological improvements.

MGMT immunorepression was documented in 23 of the 30 patients. A high level of labeling was seen in six instances, an intermediate level in six instances, and a low level in 11 instances. Only one of six patients with high MGMT immunorepression responded to temozolomide. Two tumors with intermediate MGMT immunorepression did not respond, whereas nine of the 11 tumors with low-level MGMT immunorepression responded favorably.

### Pituitary carcinomas

Pituitary carcinomas are difficult to manage given their relentless growth and metastatic spread, despite the effects of multimodality therapy. The latter includes repeated surgeries, pharmacological manipulation, radiotherapy, and conventional chemotherapy (3,49), including various combinations of *cis*-platinum, etoposide and/or paclitaxel, but these have failed to achieve favorable clinical responses (2).

Initial reports of the successful use of temozolomide to treat pituitary carcinomas appeared in 2006 (5,6). To date, 16 cases have been treated (5,6,13,16,17,21-23,25). The time between disease presentation to temozolomide administration was 5–23 years (mean: 10.7 years). The group included nine PRL-producing tumors, five ACTH-producing tumors, three clinically non-functional tumors, and three silent corticotroph carcinomas. Eleven of the 16 patients (69%) experienced a clinical and radiological response to temozolomide. Assessment of MGMT immunorepression was only

available in 11 patients; only one patient with high-level immunoexpression responded to treatment.

### Morphological changes

Morphological comparisons of pathology before and after temozolomide treatment were performed in three cases: all were patients with adenomas. One was a non-responder who exhibited no changes (10) and two were responders (8,23) whose tumors after treatment demonstrated hemorrhage, necrosis, focal fibrosis, inflammatory infiltrates, fewer mitoses, and a low Ki-67 labeling index, as well as neuronal transformation. The latter is considered to be a metaplastic phenomenon and has been observed in a variety of untreated endocrine neoplasms, including GH cell adenomas (50).

## DISCUSSION

### Response to treatment

In patients who respond to temozolomide, three basic patterns of radiographic changes are seen on MRI: tumor necrosis and hemorrhage (7,8), cystic change (19), and shrinkage (9,11-14). Such changes may be seen as early as two months after the onset of treatment.

In the tumors that respond to temozolomide, the clinical response is rapid and associated with prompt decreases in chiasmatic compression and mass effects. In patients with endocrine-active PRL- and ACTH-producing tumors, an almost immediate reduction in plasma hormone levels becomes apparent after commencement of therapy. Thus, it is possible to quickly evaluate the treatment response.

### MGMT immunoexpression and MGMT promoter methylation

The inverse relationship between MGMT immunoexpression and temozolomide response was first reported in two patients with aggressive pituitary adenomas (10). The observation was subsequently confirmed by McCormack et al. who assessed MGMT immunoreactivity in a PRL cell carcinoma and an aggressive GH-producing adenoma (13). In both studies, tumors with low-level MGMT immunoexpression demonstrated clinical and radiological responses to temozolomide therapy. Other authors have reported similar findings (51). Thus, the demonstration of MGMT immunoreactivity appears to be useful for predicting the response of aggressive pituitary adenomas and carcinomas to temozolomide treatment.

The reports of Kovacs et al. (10) and McCormack et al. (13,51) underscore the inverse relationship between MGMT immunoexpression and the efficacy of temozolomide therapy, and this relationship has also been noted in high-grade gliomas (46-48,52). Whereas the standard method for evaluating MGMT status in gliomas is the identification of promoter methylation (47), immunohistochemical detection of MGMT expression is an attractive alternative. It represents an inexpensive, readily accessible technology that is available to most laboratories (53,54). Whereas most reports pertaining to gliomas and temozolomide therapy are based on promoter methylation status, data relating to pituitary neoplasms are based on MGMT immunoexpression (24,51). Although several recent reports of aggressive pituitary tumors that were successfully treated with temozolomide have reported absent or low immunohistochemical expression of MGMT as a factor, one patient whose tumors exhibited higher levels of MGMT staining also experienced

clinical improvement and tumor shrinkage following treatment (23). It is of note that some tumors with no promoter methylation also respond to therapy (22,23). These observations challenge the notion that MGMT promoter methylation is a reliable predictor of treatment response. Indeed, two recent studies on MGMT promoter methylation and the temozolomide response in eight aggressive adenomas and seven pituitary carcinomas found no association between promoter methylation status and response (22,23). Salehi et al. (55) did not find a close correlation between MGMT immunoexpression and MGMT promoter methylation in a study on aggressive pituitary adenomas and carcinomas. Thus, the utility of MGMT promoter methylation for the selection of patients who might respond well to temozolomide treatment remains controversial and an active focus of further research. The problem is that many tumors possess an admixture of MGMT immunopositive and immunonegative cells. Obviously, in such instances, it is difficult to predict overall the response to temozolomide.

To date, MGMT immunoexpression has been documented in 23 adenomas and 11 carcinomas. In 18 tumors, MGMT labeling was low and correlated with a good therapeutic response to temozolomide (14/18 cases). In eight instances, MGMT staining was intermediate: five tumors responded well and three did not. In eight patients with high MGMT immunoexpression, only one responded positively. Thus, tumors featuring low- and intermediate-level MGMT immunoexpression ( $n=26$ ), when compared with those with high MGMT immunoexpression ( $n=8$ ), showed a good response to temozolomide in 19/26 (73%) versus 1/8 (13%) cases ( $p=0.0039$ ; two-tailed Fisher's exact test).

### Suggested indications for using temozolomide treatment

Based on the published cases and the reported response rates, temozolomide therapy can be recommended when other options fail, particularly in the following instances: (1) aggressive PRL-producing tumors that are resistant to bromocriptine or cabergoline and continue to grow after surgery and radiotherapy; (2) aggressive ACTH-producing tumors, especially Crouse cell and Nelson syndrome variants that cannot be cured by surgery and radiotherapy; (3) recurrent, clinically non-functional tumors exhibiting continued growth after repeated surgeries and radiotherapy; (4) pituitary carcinomas.

Temozolomide has been documented as valuable for the treatment of aggressive pituitary adenomas and carcinomas. The clinical and radiological responses are encouraging: 60% of aggressive adenomas and 69% of pituitary carcinomas respond well to treatment. An inverse correlation exists between MGMT immunoexpression and the therapeutic response to temozolomide. Based upon our literature review, a significant proportion of the adenohypophyseal tumors that are responsive to temozolomide show low-level MGMT immunoexpression, whereas only one tumor showing high-level immunoexpression was found to respond. The use of immunohistochemistry for determining MGMT immunoexpression appears to be a promising guide for therapeutic decision-making (13,53). Obviously, all available methods for assessing the likelihood of a positive temozolomide response should be utilized. We feel strongly that the determination of MGMT immunoreactivity is of clinical value and that MGMT promoter methylation status should



be determined as well. The molecular mechanisms that affect *MGMT* expression remain to be fully elucidated. Targeted modulation of *MGMT* may be used in patients who may otherwise not respond to temozolomide therapy. Future therapies that incorporate different dosing regimens or other drugs may improve the tumor responsiveness.

## DISCLOSURE

The authors have no personal financial or institutional interest in any pharmaceutical agents or testing devices described herein.

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## AUTHOR CONTRIBUTIONS

Ortiz LD, Syro LV, Scheithauer BW, and Kovacs K conceived the study and wrote the manuscript. Ortiz LD, Syro LV, and Rotondo F searched the literature and extracted the data. Rotondo F, Uribe H, Fadul CE, and Horvath E contributed to the initial version of the manuscript. All authors contributed to the critical revision of the manuscript and approved the final version.

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